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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/697,473	CHOPRA, SHAM	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-28 are currently pending and are the subject of this Office Action. This is the first Office Action on the merits of the application.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §§ 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application(s) (the parent or original non-provisional application and/or provisional application). The disclosure of the invention in the parent application(s) and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application(s), Application Nos. 60/293,701 (filed 5/25/2001), 10/085,234 (filed 2/28/2002) and 10/430,142 (filed 5/6/2003), fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of this application. In the instant case, the prior-filed applications fail to provide adequate support for the instantly claimed chronotherapy tablet having a substantially oblong core, including the specific formulations and embodiments recited in the dependent

claims. Further, the doses recited in claims 15-16, 19-20 and 23 are not supported in any of the prior-filed applications.

As such, the earliest effective U.S. filing date of the instant claims has been determined to be 10/30/2003, the filing date of the instant application.

Information Disclosure Statement

Examiner has considered the information disclosure statement (IDS) submitted on 5/1/2006 to the extent that each reference cited therein is a proper citation. Please see attached USPTO Form 1449.

Drawings

The replacement drawings were received on 3/30/2004. These drawings are acceptable and of sufficient quality to allow for examination.

Claim Objections

Claim 12 is objected to under 37 CFR § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 12 depends from claim 2, which depends from claim 1. Claim 2 recites a chronotherapy tablet comprising two layers of pharmaceutical compositions. Claim 12 recites the limitation wherein the chronotherapy tablet according to

claim 2 comprises at least three layers of pharmaceutical compositions. Claim 12 therefore expands, rather than further limits claim 2 from which it depends.

Applicant is advised that should claim 5 be found allowable, claim 7 will be objected to under 37 CFR § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

In the instant case, claims 13 and 26 recite "an acetic acid derivative", "an indole derivative", "an oxicam", "a propionic acid derivative", "a tiaprofenic derivative" and a "salicylic acid derivative". There is insufficient written basis for these limitations in the claims.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

The specification does not describe any structural features, methods of identifying, methods of synthesizing or methods of isolating the instantly claimed derivatives. Further, the scope of the claim limitations is not apparent, as the term "derivative" has not been defined in the specification. As such, it is not evident that applicant was in possession of any derivatives of acetic acid, indole, propionic acid, tiaprofenic or salicylic acid at the time of the invention, other than the derivatives explicitly named in the disclosure.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 17 and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the limitation "the first layer" in line 1 (claims 9 and 17) and line 4 (claim 26). There is insufficient antecedent basis for this limitation in the claims.

Claims 18-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, claim 18 depends from claim 13, which depends from claim 9. Claim 9 recites a chronotherapy tablet wherein the first layer is a delay layer. Claim 18 recites the limitation wherein the first layer comprises a therapeutically effective amount of diltiazem. It is not clear how the first layer can be a delay layer and comprise a drug, because claim 13 requires that the second and third layers comprise a drug, but not the first layer.

Claims 19 and 21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what is meant by the phrase "substantially completely releasable". Something is either completely releasable or it is not completely releasable. It cannot be "substantially completely" releasable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 10-12 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Conte *et al.* (U.S. Patent No. 4,865,849; Issued Sep. 12, 1989) (cited by applicants).

The instant claims are drawn to a tablet comprised of at least two superposed layers of different compositions and wherein a coating envelops the core except for at least one exposed release face of the core at at least one end of the core.

Conte *et al.* teach a tablet for pharmaceutical use able to release active substances at successive times, comprising a first layer containing a portion of active substance, a barrier layer which is interposed between the first layer and the third layer containing the remaining portion of active substance (Abstract). Said barrier layer and third layer are housed in a casing, thereby allowing the part of active substance not inserted into the casing to be immediately available for dissolving (*id.*). The reference thus teaches the limitations of instant claims 1-3, 5, 7-8 and 11.

With respect to instant claims 4, 6, 9-10, 12 and 17 Conte *et al.* teach that the tablet can consist of more than two deposits of active substance separated from each other by layers of polymeric material (*i.e.* barrier or delay layers) (col. 2, lines 11-19; Claim 6). The reference further teaches that the active substance can be of the same or different types in the various deposits of active material (*id.*; Claims 7 and 8). Conte *et al.* explicitly teach tablets comprising ibuprofen (Example 1), propanolol HCl (Example 2), indomethacin (Example 3) and naproxen (Example 4) as the active ingredients therein.

With respect the instantly claimed limitation wherein the delay layers provide for substantially complete dissolution of the delay layers to require between about 5 to about 9 hours (*e.g.* claim 17), the reference utilizes identical polymers to form the barrier layer as the instantly claimed tablets. For example, applicants describe "dissolution rate modifiers" that include hydroxypropylmethylcellulose (page 17, lines 25-28). Conte *et al.* teach that the barrier layer of their tablets comprises hydroxypropylmethylcellulose (col. 4, lines 33-45). Conte *et al.* further

teach that the barrier layer slowly hydrates, with an increase in volume of the barrier, gelling and weakening of the layer and slow erosion and/or solubilization (col. 5, lines 38-41). The barrier layer becomes progressively permeable to the disintegration liquid, to enable water, after a time of about 0.5 to 1 hours, to come into contact with the second layer of the system (*id.*, lines 42-46). The reference thus inherently teaches the limitation wherein the delay layer substantially dissolves in about 5 to 9 hours. This is because the barrier layer taught in Conte *et al.* is comprised of the same material as the "delay layer" instantly claimed. As such, the properties of that material (*i.e.* dissolution rate) will be the same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849) (cited by applicants).

Instant claim 9 recites a tablet multilayer tablet wherein the first layer is a delay layer. Claim 13 recites a tablet according to claim 9 comprising additional layers of active ingredient. Claims 14-16 recite a tablet comprising the drug naproxen.

Conte *et al.* disclose as discussed *supra*. With respect to claim 9, Conte *et al.* disclose that the tablet taught therein can consist of more than two deposits (*i.e.* layers) of active substance separated from each other by layers of polymer material (*i.e.* delay or barrier layers)

(col. 2, lines 11-19; Claim 6). Further, the active substance can be in the form of a single layer separated from the external environment by a layer of gellable and/or soluble polymer material (*id.*). As such, it would have been *prima facie* obvious to modify the tablet of Conte *et al.* to form a tablet comprising a first layer that is a delay layer (claim 9) and additional layers comprising active substance. With respect to claim 13, the reference discloses tablets comprising the instantly claimed drugs (see Examples). The reference further discloses tablets with multiple layers of active substances separated by one or more barrier layers. As such, it would have been *prima facie* obvious to about formulate a multilayer tablet with a first layer that is a delay layer and subsequent layers containing active substances. This is especially true given that the reference explicitly contemplates a tablet wherein the active substances are separated from the external environment by a barrier layer (col. 2, lines 11-19).

With respect to claims 14-16, Conte *et al.* disclose a tablet comprising naproxen in a dose of 275 mg per layer (Example 4). Naproxen is "substantially completely releasable" in about 15 minutes as instantly claimed (e.g. 78% in 10 minutes and 88% in 15 minutes) (col. 12, lines 50-60). With respect to the third layer of naproxen being released as a constant rate over a period of about 5 hours, modifying the formulation of naproxen in said third layer would have been well within the level of ordinary skill in the art. It is noted that the prior art discloses various methods of modifying the release rate of drugs from pharmaceutical compositions. Conte et *al.* specifically disclose that the rate of release of active substance from the layers containing it can be varied according to therapeutic needs by varying the composition of the layer concerned (col. 2, lines 61-64). For example, polymers, such as hydroxypropylmethylcellulose, can be added to the active drug layer to effect differing dissolution and release rate profiles (col. 3, lines 4-11).

As such, applicant's instantly claimed release profile amounts to routine optimization of the prior art compositions. The motivation to modify the reference compositions to attain specific release rates of active substances is found in Conte *et al.* wherein they disclose that the rate of release of active substance can be modified to effect differing dissolution and release rate profiles.

Claims 18-20, 24-25 and 27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849) (cited by applicants) in view of Geoghegan *et al.* (U.S. Patent No. 5,219,621; Issued Jun. 15, 1993).

Conte *et al.* disclose as discussed *supra*. The reference does not explicitly disclose a multilayer tablet formulation comprising the drug diltiazem.

However, Geoghegan *et al.* is provided as evidence that diltiazem is often formulated in a tablet dosage unit and further provides evidence that sustained release of diltiazem is advantageous. The reference discloses that diltiazem is a benzothiazine derivative possessing calcium antagonist activity (col. 1, lines 18-21). It is further disclosed that diltiazem has been shown to be useful in alleviating symptoms of chronic heart disease, particularly angina pectoris and myocardial ischemia and hypertension (*id.* at lines 21-27). Diltiazem is conventionally administered in tablet form (30 mg and 60 mg) as diltiazem HCl (*id.* at lines 27-29). Geoghegan *et al.* disclose a diltiazem pellet formulation for oral administration comprising a diltiazem core with a multi-layer membrane surrounding the core (Abstract). The number of layers in the membrane and the ratio of polymers are effective to permit release of diltiazem over an extended period of time (col. 2, lines 42-55). Diltiazem was administered to patients in a dose of 120 mg and reference diltiazem tablets at a dose of 60 mg (col. 12, lines 43-50).

With respect to the instantly claimed doses of diltiazem, the limitations "between about 25 mg – 100 mg" (claim 19), "between about 50 mg – 150 mg" (claim 20) and "between about 80 mg – 200 mg" (claim 21) are rendered obvious by the doses of 60 mg and 120 mg diltiazem that were administered to patients in Geoghegan *et al.*

With respect to the methods recited in claims 24-25 and 27, it is well known in the art that diltiazem is useful in the treatment of cardiovascular disease. As such, because the treatment of cardiovascular disease with diltiazem was well known in the art, it would therefore have been prima facie obvious at the time of the invention to use the instantly claimed dosage forms of diltiazem to treat cardiovascular disease.

Thus, it would have been *prima facie* obvious at the time the invention was made to formulate a multi-layer tablet as disclosed in Conte *et al.* with the drug diltiazem and use said tablet to treat a patient with cardiovascular disease. Geoghegan *et al.* provide evidence that diltiazem dosage units were known in the art and useful in the treatment of cardiovascular disease. As such, the skilled artisan would have been imbued with at least a reasonable expectation that diltiazem could be used in the multi-layer tablet disclosed in Conte *et al.* The substitution of one drug for another in a prior art drug formulation would have been *prima facie* obvious to the skilled artisan.

Claims 24-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849) (cited by applicants) in view of Dunn *et al.* (U.S. Patent No. 4,525,345; Issued Jun. 25, 1985).

Conte *et al.* disclose as discussed *supra*. The reference does not explicitly disclose a method of treating arthritis.

However, Dunn *et al.* disclose a constant rate indomethacin formulation comprising 50 to 200 mg indomethacin (Abstract). Indomethacin, naproxen, and ibuprofen are recited as treatments of choice for arthritic patients (col. 1, lines 23-26). The reference further discloses a method of treating arthritis comprising administering an oral dosage form of indomethacin to a patient (claim 25).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the indomethacin multi-layer tablet disclosed in Conte *et al.* to a patient suffering from arthritis. The skilled artisan would be motivated to do so because indomethacin is an art recognized treatment for arthritis as disclosed in Dunn *et al.* As such, the skilled artisan would have been imbued with at least a reasonable expectation that administration of a multi-layer indomethacin tablet to a patient suffering from arthritis would be an effective treatment.

Claims 21-25 and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849) (cited by applicants) in view of Le Roux *et al.* (Respiration, 1991, vol. 58, pages 192-197).

Conte *et al.* disclose as discussed *supra*. The reference does not explicitly disclose a multilayer tablet formulation comprising the drug salbutamol or a method of treating asthma.

However, Le Roux *et al.* is provided as evidence that the instantly claimed doses and method of treating asthma with salbutamol were known in the art. Le Roux *et al.* disclose that a

slow-release oral formulation of salbutamol (standard oral dose of 4 mg) was administered to asthma patients (Abstract). An 8 mg slow-release oral formulation of salbutamol was also administered to asthma patients (*id.*). It is noted that the 8 mg dose of oral salbutamol was more effective than the 4 mg dose.

With respect to the instantly claimed dose of salbutamol, the limitations "between about 2 mg to about 4 mg" (claim 23) are rendered obvious by the doses of 4 mg and 8 mg salbutamol that were administered to patients in Le Roux *et al.* Le Roux *et al.* also provide further motivation to administer a multi-layer tablet of salbutamol because they disclose that an oral dose of 8 mg was more effective than an oral dose of 4 mg. As such, the skilled artisan would have been motivated to administer salbutamol in a dosage form that would lead to multi-phase release profile of the drug.

With respect to the methods recited in claims 24-25 and 28, it is well known in the art that salbutamol is useful in the treatment of asthma. As such, it would have been *prima facie* obvious at the time of the invention to use the instantly claimed dosage forms of salbutamol to treat asthma.

Thus, it would have been *prima facie* obvious at the time the invention was made to formulate a multi-layer tablet as disclosed in Conte *et al.* with the drug salbutamol and use said tablet to treat patients with asthma. Le Roux *et al.* provide evidence that oral salbutamol dosage forms were known in the art and used to treat asthma patients. As such, the skilled artisan would have been imbued with at least a reasonable expectation that salbutamol could be used in the multi-layer tablet disclosed in Conte *et al.* The substitution of one drug for another in a prior art drug formulation would have been *prima facie* obvious to the skilled artisan.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

December 29, 2006

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER